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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/761,169	01/20/2004	Ali O. Gure	L0461.70073US01	3734

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EXAMINER	
REDDIG, PETER J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 06/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/761,169	GURE ET AL.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *6,9,10 and 13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,8,11,12 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/20/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election

1. The Election filed 04/21/06 in response to the Office Action of 04/13/06 is acknowledged and has been entered.

Applicant's election with traverse of Group I, claims 1-14 and SEQ ID NO: 4 (SOX1) is acknowledged. The traversal is on the ground(s) that a search and examination of all of the inventions would not impose a serious burden on the examiner. The applicant argues that, "The claims are limited in terms of (1) the nucleic acid sequences, (2) the method is a diagnostic method, and (3) the diagnostic method includes determining the presence or level of antibodies that bind proteins produced by the listed nucleic acid molecules." Furthermore, the applicant argues that, "In addition, for claims 11-13, the diagnostic methods include the use of a plurality of proteins to determine the presence or level of antibodies. The restriction of the claims to a single sequence might be viewed as effectively negating the ability to claim the use of a plurality of proteins in the methods."

The argument drawn to items (1), (2) (3) have been considered but have not been found persuasive because there are approximately eight different databases that accompany the results of a search of one discrete amino acid or nucleotide sequence and each result set from a particular database must be carefully considered. Hence, the search of five different amino acid sequences, and different amino acid segments in the databases would require extensive searching and review.

Although the inventions are classified similarly, the classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not coextensive and is much more important in evaluating the burden of search. This search would have to be performed five times for each claimed sequence. For these reasons, the restriction requirement between SEQ ID NOs is deemed to be proper.

However, the argument regarding the need for a plurality of proteins for claims 11-13 has been considered and has been found persuasive therefore the original restriction requirement, dated April 13, 2006, is hereby withdrawn.

During a telephone conversation with John R. Van Amsterdam on May 30,2006, a new restriction of the claims into two groups was described to the applicant:

I. Claims 1-10 and 14, drawn to a method of contacting a biological sample isolated from a patient with ONE claimed, isolated protein that binds an antibody in the sample encoded by a nucleic acid molecule selected from the group consisting of SOX2 (SEQ ID NO: 3), SOXI (SEQ ID NO: 4), ZlC2 (SEQ ID NO: 5), SOX3 (SEQ ID NO: 11), and SOX21 (SEQ ID NO: 12) for determining regression, progression, or onset of cancer, classified in class 435, subclass 7.1.

II. Claims 11-13, drawn to a method of contacting a sample with a plurality of proteins or peptides that selectively bind antibodies that selectively bind a plurality of proteins or peptides encoded by a nucleic acid molecule selected from the group consisting of SOX2 (SEQ ID NO: 3), SOXI (SEQ ID NO: 4), ZlC2 (SEQ ID NO: 5), SOX3 (SEQ ID NO: 11), and SOX21 (SEQ ID NO: 12), classified in class 435, subclass 7.1.

In a telephone interview John R. Van Amsterdam, on June 1, 2006, made a provisional election with traverse to prosecute the invention of Group II, claims 11-13 and electing SOX1 (SEQ ID NO: 4) and ZIC 2 (SEQ ID NO: 5).

Applicant in replying to this Office action must make affirmation of this election.

Based on the election of SEQ ID NO: 4 and SEQ ID NO: 5, which are common to both Groups I and II, the search for the inventions of both Groups I and II, as drawn only to auto-antibodies against the polypeptides encoded by SEQ ID NO: 4 and 5, was found not to be burdensome. Thus the claims of Groups I and II as drawn only to auto-antibodies against the polypeptides encoded by SEQ ID NO: 4 and SEQ ID NO: 5 are hereby rejoined by the examiner and all of the claims are examined with the elected SEQ ID NOs, SEQ ID NO: 4 and SEQ ID NO: 5.

During this conversation the applicant requested a search of all SEQ ID NOs as claimed in the method. However, the request was denied for the reasons of record.

2. Claims 1-14 are pending.

Claims 6, 9, 10, and 13 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

Claims 1-5, 7, 8, 11, 12, and 14 are currently under consideration.

Specification Objections

3. The abstract of the disclosure is objected to because of the use of the legal phraseology "inter alia". Correction is required. See MPEP § 608.01(b).

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

Appropriate correction is required.

4. The disclosure is objected to because of the following informalities:

The specification on page 1 should be amended to reflect the status of the parent application serial number 09/489,101. It should state:

This application is a divisional of U.S. application serial number 09/489,101, filed January 21, 2000, now abandoned, the disclosure of which is incorporated by reference herein in its entirety.

There is a grammatical error on page 21, line 31; "generated" should be "generate".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-5, 7, 8, 11, 12, and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for determining the presence of antibodies to SEQ ID NO: 4 and/or 5 as drawn to determining the onset of cancer, does not reasonably provide

enablement for the prediction/prognosis as to the progression or regression of cancer by determining the presence of antibodies to SEQ ID NO: 4 and/or 5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are broadly drawn to a method for determining regression, progression, or onset of cancer, comprising contacting a biological sample isolated from a patient, who has or is suspected of having the cancer, with a protein or peptide that binds an antibody, wherein the antibody selectively binds a protein or peptide encoded by a nucleic acid molecule selected from the group consisting of SEQ ID NO: 4 and/or 5, and determining the presence of the antibody as an indication of regression, progression, or onset of cancer.

This means that the method defined by the claims can diagnose not only the onset of cancer, but also the progression and/or regression of the cancer by determining the presence of antibodies to the proteins or peptides encoded by SEQ ID NO: 4 and/or 5. Furthermore, the method as broadly claimed reads on the prediction/prognosis as to the progression or regression

of the cancer by determining the levels of antibodies to the proteins or peptides encoded by SEQ ID NO: 4 and/or 5.

The specification teaches that sera from 17 SCLC patients were examined for antibodies that could be bind proteins or peptides encoded by SEQ ID NO: 4 and SEQ ID NO: 5. For SEQ ID NO: 4, 7 of 17 patients (41%) were positive for antibodies at variable titers to the protein or peptides encoded by SEQ ID NO: 4. For SEQ ID NO: 5, 5 of 17 patients (29%) were positive for antibodies at variable titers to the protein or peptides encoded by SEQ ID NO: 5. No reactive antibodies to the proteins or peptides encoded by SEQ ID NO: 4 and/or 5 were detected in the sera from 16 normal patients (Example 5, pp. 60-62, and p. 61, Table 3).

The specification teaches that the high frequency of sera positive for SEQ ID NO: 4 and 5 and the high titers of the sera is striking. It teaches that most antigens tend to have detectable seral antibody in only 20-25% of tumor patients, rarely exceeding 25 %. Given the above, the specification teaches that the claimed antibody-based assay can be useful in the diagnosis of SCLC. The specification also speculates that these assays can be correlated to the clinical progression/remission of the disease (p.61, 2nd para. and p. 62, 1st para.).

One cannot extrapolate the teaching of the specification to the scope of the claims because the presence of the antibody alone does not tell you anything more than that the antigen has been expressed and nothing at all about whether it is currently being expressed or is involved with regression or progression. Janeway and Travers (Immunobiology: The Immune System in Health and Disease, 1994, pp. 9:40-41, Fig. 9.35) teach that this is because upon exposure to an antigen, the immune system has an immunological memory and the presence of antibodies and the cells that produce them does not correlate to the continued presence of the antigen. The

memory is sustained by long lived lymphocytes reactive to the antigen which are maintained through the life of an animal and also by the re-stimulation of these lymphocytes by small amounts of the original antigen or cross reactive antigens. Thus, the presence of antibody does not necessarily indicate the presence of the antigen to which it is directed.

Additionally, Janeway and Travers (Immunobiology: The Immune System in Health and Disease, 1994, pp. 9:42, Fig. 9.37) teach that the affinity of antibodies changes upon repeated exposure to the antigen. Thus, measuring the titer of the antibodies to the antigen as described in the specification would not necessarily be indicative of the level of the antibodies present if the affinity of the antibodies is variable.

Furthermore, the claims as currently constituted read on the prediction/prognosis of progression or regression of disease and the specification provides neither guidance on nor exemplification of how to correlate the level of the SOX1 or ZIC2 antibodies with the ability to provide a prognostic evaluation of a patient having cancer. Tockman et al. (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection using protein biomarkers the basic principles taught are clearly applicable to other oncogenic markers including antibodies to tumor antigens as biomarkers for lung cancer progression and regression. Tockman et al. teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and

if validated (emphasis added) can be used for population screening (p. 2713s, col. 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col. 2). In addition, Slamon et al. (Science Vol. 235, January 1987, pages 177-182) teach other essential factors that are known to be important in the prognosis of breast cancer in individual patients such as size of the primary tumor, stage of the disease at diagnosis, hormonal receptor status, and number of axillary lymph nodes involved with disease (page 178, 1st column, 2nd paragraph). Such data are critical to assessing actuarial curves for relapse (Figure 3), and for comparing disease-free survival and overall survival to prognostic factors (Table 4). In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable that the invention, as broadly claimed, could be used with a reasonable expectation of success.

6. If applicant were able to overcome the rejections set forth above, Claim1-5, 7, 8, 11, and 12 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while

being enabling for assessing SOX1/ZIC2 auto-antibodies in SCLC patients for the determining regression progression or onset of SCLC, does not reasonably provide enablement for assessing SOX1/ZIC2 auto-antibodies in **any** type of cancer for the determining regression progression or onset of any type of cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to method for determining regression, progression or onset of cancer, comprising contacting a biological sample isolated from a patient, who has or is suspected of having the cancer, with a protein or peptide that binds an antibody, wherein the antibody selectively binds a protein or peptide encoded by SEQ ID NO:4 AND/OR SEQ ID NO:5 and determining the presence or level of the antibody as an indication of regression, progression or onset of the cancer, wherein the sample is a body fluid, a body effusion or a tissue, wherein the sample is blood or serum, wherein the protein or peptide that binds the antibody is a detectable protein or peptide, wherein the detectable protein or peptide is labeled with a radioactive label or an enzyme, wherein at least one of the plurality of proteins bound by the antibodies is encoded by ZIC2 (SEQ ID NO:5).

This means that the claimed method is drawn to determination of regression, progression, or onset of cancer for **any** form of cancer.

The specification teaches that sera from 17 SCLC patients were examined for antibodies that could be bind proteins or peptides encoded by SEQ ID NO: 4 and SEQ ID NO: 5. For SEQ ID NO: 4, 7 of 17 patients (41%) were positive for antibodies at variable titers to the protein or peptides encoded by SEQ ID NO: 4. For SEQ ID NO: 5, 5 of 17 patients (29%) were positive

for antibodies at variable titers to the protein or peptides encoded by SEQ ID NO: 5. No reactive antibodies to the proteins or peptides encoded by SEQ ID NO: 4 and/or 5 were detected in the sera from 16 normal patients (Example 5, pp. 60-62, and p. 61, Table 3).

The specification teaches that the high frequency of sera positive for SEQ ID NOs: 4 and 5 and the high titers of the sera is striking. It teaches that most antigens tend to have detectable seral antibody in only 20-25% of tumor patients, rarely exceeding 25 %. Given the above, the specification teaches that the claimed antibody-based assay can be useful in the diagnosis of SCLC. The specification also speculates that these assays can be correlated to the clinical progression/remission of the disease (p.61, 2nd para. and p. 62, 1st para.).

One cannot extrapolate the teaching of the specification to the scope of the claims because it is recognized that cancer is a complex disease with varied etiologies for a given cancer type. Many different types of polypeptide expression patterns characterize different cancers. For example, studies using variations of the claimed method demonstrate the varied pattern of genes with autologus sera in different cancer types. Using the SEREX method, Scanlan et al. (Int. J. Cancer, 1998, 76: 652-658, IDS) identified a panel of genes with autologous sera (Table 1A & 1B) in colon cancer that is distinct from those identified by Chen et al. (PNAS, 1998, 95: 6919-6923, IDS) in testicular cancer, see Table 1, or the genes identified in the instant application.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the stare of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application,

as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the broadly claimed method would function as claimed with a reasonable expectation of success based only on the showing that sera of SCLC patients is found to contain antibodies to the novel SOX1 and ZIC2 polypeptides. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

7. No claims are allowed.

8. The claims are free of the prior art. The closest prior art is Sahin, et al. (PNAS, 1995, 92: 11810, IDS) that does not teach or suggest the limitation wherein the detected antibody binds to

SOX1 (SEQ ID NO: 4) or ZIC2 (SEQ ID NO: 5) or the limitation of using this method as an indication of regression, progression, nor onset of cancer.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Peter J. Reddig, Ph.D.
Examiner
Art Unit 1642

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

PJR